



Review Article

Diuretic Resistance in Advanced Heart failure: A Literature Review

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ABSTRACT

Background : Diuretic resistance is a common problem issue in acute decompensation of advanced heart failure

Objective : In this review, we will discuss how to diagnose the advanced heart failure and the underlying mechanism of diuretic resistance in heart failure patients. We also describe pharmacological and non-pharmacological strategies to overcome this issue.

Discussion : Advanced heart failure (HF) is used to characterize patients in HF with severe symptoms, recurrent decompensation and severe cardiac dysfunction. Most of HF hospitalization are due to signs and symptoms of fluid overload. Recurrent congestion could worsen patients outcomes. Loop diuretics are recommended for the treatment of congestion in HF patient. However, diuretic resistance is a common problem issue in acute decompensation of advanced chronic heart failure (ACHF) patients and established prognostic factor. The pathophysiology of diuretic resistance is very complex, and several etiologies may be involved. It derives from multiple factors, including reduced delivery of the diuretic to its luminal site of action, neurohormonal activation, tubular compensatory adaptation, and drug interactions

Conclusion : Diuretic resistance has emerged as an independent factor behind worse HF patient outcomes, namely in-hospital worsening, early post-discharge mortality, and rehospitalizations. Once the diuretic resistance has been treated successfully, the treatment of advanced HF should be optimized in order to reduce further morbidity and mortality.

1. Introduction

Heart failure (HF) is a clinical syndromes that is characterized by typical symptoms such as breathlessness, ankle swelling, and fatigue. Signs may be accompanied by consisted of elevated jugular venous pressures (JVP), pulmonary crackles, and peripheral edema which can cause a structural and/or functional cardiac abnormality, resulting in reduced cardiac output and/or elevated intracardiac pressures at rest or during stress. Advanced HF is used to characterize patients with severe symptoms, recurrent decompensation, and severe cardiac dysfunction problem.¹

The prevalence of HF is approximately 1-2% of the adult population in developed countries and increase more than 10% among people >70 years of age, whereas estimated the prevalence of patients with advanced heart failure is about 1% until 10% of the overall heart failure population. It was predicted to increase because of the growing number of patients with heart failure and their better treatment and survival rate.²

Most of the HF hospitalizations are due to signs and symptoms of fluid overload. Recurrent congestion could worsen patients outcomes. Loop diuretics are recommended for the treatment of congestion in heart failure patient. Diuretic therapy is mainly described in the current guidelines for HF treatment. However, diuretic resistance is a common problem issue in acute decompensation of advanced chronic heart failure (ACHF) patients and established prognostic factor. Some early report estimated the prevalence of diuretic resistance about 20 %-30% in HF patients population.³

In this review, we will discuss how to diagnose the advanced heart failure and the underlying mechanism of diuretic resistance in HF patients. We also describe pharmacological and non-pharmacological strategies to overcome this issue.

2. Discussion

2.1 Advance Heart Failure

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2.2.1 Definition of Advanced Heart Failure

The definition of advanced HF is evolved time by time to have better comprehension directing clinicians to diagnose. On ESC 2007, advanced HF emphasizes patients who remain severely symptomatic despite optimal guideline-directed management regardless of left ventricular ejection fraction (LVEF), including patients with advanced HF who remain ambulatory but are essentially RV failure (e.g., ARVC) or non-operable severe valve abnormalities or congenital abnormalities or persistently high (or increasing) BNP or NT-proBNP values and data of severe diastolic dysfunction or LV structural abnormalities according to the ESC definition of the HFpEF and HfmrEF.⁵ Then for Third, episodes of pulmonary or systemic congestion requiring high-dose intravenous diuretics (or diuretic combinations), episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing more than 1 unplanned visit or hospitalization in the last 12 months. Furthermore, the fourth severe impairment of exercise capacity with the inability to exercise or low 6MWT (<300 m) or pVO₂ ($<12 - 14$ mL/kg/min), estimated to be of cardiac origin.⁴

In 2018, ESC updated the definition of advanced HF with four categories. For the first, severe and persistent symptoms of heart failure (NYHA class III (advanced) or IV). Second, severe cardiac dysfunction defined by a reduced LVEF $\leq 30\%$, isolated RV failure (e.g., ARVC) or non-operable severe valve abnormalities or congenital abnormalities or persistently high (or increasing) BNP or NT-proBNP values and data of severe diastolic dysfunction or LV structural abnormalities according to the ESC definition of the HFpEF and HfmrEF.⁵ Then for Third, episodes of pulmonary or systemic congestion requiring high-dose intravenous diuretics (or diuretic combinations), episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing more than 1 unplanned visit or hospitalization in the last 12 months. Furthermore, the fourth severe impairment of exercise capacity with the inability to exercise or low 6MWT (<300 m) or pVO₂ ($<12 - 14$ mL/kg/min), estimated to be of cardiac origin.⁶

2.2.2 Detecting Congestion in Heart Failure

Congestion in HF can be defined as signs and symptoms of extracellular fluid accumulation that result in increased cardiac filling pressures. Filling pressures are the integrated result of the cardiac systolic and diastolic function, plasma volume, and venous capacitance/compliance. HF with increased neurohumoral activation induces a state of increased renal sodium and water avidity resulting in an increased plasma volume. Also, increased sympathetic output leads to splanchnic arterial and venous constriction resulting in blood redistribution from the splanchnic capacitance vasculature to the circulatory volume. This increases the adequate circulating volume by redistribution, in a state where volume expansion is already present.⁷

Physical signs and symptoms of congestion are based on detecting increased filling pressures and/or the extravascular fluid build-up secondary to the increased filling pressures. As such, the jugular venous pressure (JVP) is the most useful physical finding for determining a patient's volume status. Not only does a JVP detect systemic congestion, but there is good sensitivity (70%) and specificity (79%) between high JVP and elevated left-sided filling pressure. Changes in JVP with therapy usually parallel changes in left-sided filling pressure, although significant inter-observer variability regarding the extent of JVP elevation exists. Also, while a chest X-ray can show signs of lung congestion and pleural fluid, 20% of patients with congestion exhibit a normal chest X-ray.⁸

In comparison to chest X-ray, lung ultrasound is better in ruling out interstitial edema and pleural effusions. Lung ultrasound detects B-lines originating from an extravasated fluid into the interstitium and alveoli. More than three B-lines in more than two intercostal spaces bilaterally are considered diagnostic for the detection of interstitial and alveolar edema in acute heart failure.⁹

Echocardiographic parameters can be used to estimate right and left-sided filling pressures, although with less certainty in acute heart failure. Estimation of right atrial pressures can be performed by assessing the collapsibility and width of the vena cava. Doppler imaging

and tissue Doppler can be used to assess left-sided filling pressures. With rising filling pressures, an increase in early diastolic mitral inflow velocities (E wave) occurs.¹⁰ This is indicative of increased filling pressures in the presence of a low e' , especially if E-wave deceleration time is short and A-wave velocities are low. Nevertheless, the use of e' might be limited in advanced heart failure. Guidelines suggest the measurement of natriuretic peptides (NPs) in all patients with acute heart failure, especially to distinguish from non-cardiac causes of dyspnoea (class I recommendation, level of evidence A). NPs have a high negative predictive value for ruling out acute heart failure with congestion [thresholds for excluding acute heart failure; B-type natriuretic peptide (BNP) <100 pg/mL, N-terminal pro BNP (NT-proBNP) <300 ng/mL and mid-regional pro atrial natriuretic peptide <120 pg/mL]. In patients with a history of heart failure or cardiac disease, the combination of signs and symptoms of congestion, indicative chest X-ray and the measurement of elevated NPs allows for the diagnosis of congestion.¹¹

2.3 Mechanism of Action of Diuretics in Heart Failure

2.3.1 Physiology Diuresis in Kidney

As blood flows through the kidney, it passes into glomerular capillaries located within the cortex (outer zone of the kidney). These glomerular capillaries are highly permeable to water and electrolytes. Glomerular capillary hydrostatic pressure drives (filters) water and electrolytes into Bowman's space and into the proximal convoluted tubule (PCT). About 20% of the plasma that enters the glomerular capillaries is filtered (termed filtration fraction). The PCT, which lies within the cortex, is the site of sodium, water, and bicarbonate transport from the filtrate (urine), across the tubule wall, and into the interstitium of the cortex. About 65-70% of the filtered sodium is removed from the urine found within the PCT (this is termed sodium reabsorption).¹² This sodium is reabsorbed isosmotically, meaning that every molecule of sodium that is reabsorbed is accompanied by a molecule of water. As the tubule dives into the medulla or middle zone of the kidney, the tubule becomes narrower and forms a loop (Loop of Henle) that reenters the cortex as the thick ascending limb (TAL) that travels back to near the glomerulus. Because the interstitium of the medulla is very hyperosmotic and the Loop of Henle is permeable to water, water is reabsorbed from the Loop of Henle and into the medullary interstitium. This loss of water concentrates the urine within the Loop of Henle.¹³

The TAL, which is impermeable to water, has a cotransport system that reabsorbs sodium, potassium, and chloride at a ratio of 1:1:2. Approximately 25% of the sodium load of the original filtrate is reabsorbed at the TAL. From the TAL, the urine flows into the distal convoluted tubule (DCT), which is another site of sodium transport ($\sim 5\%$ via a sodium-chloride cotransporter) into the cortical interstitium (the DCT is also impermeable to water). Finally, the tubule dives back into the medulla as the collecting duct and then into the renal pelvis, where it joins with other collecting ducts to exit the kidney as the ureter. The distal segment of the DCT and the upper collecting duct has a transporter that reabsorbs sodium (about 1-2% of filtered load) in exchange for potassium and hydrogen ion, which are excreted into the urine.¹⁴ It is important to note two things about this transporter. First, its activity is dependent on the tubular concentration of sodium so that when sodium is high, more sodium is reabsorbed, and more potassium and hydrogen ion are excreted. Second, this transporter is regulated by aldosterone, which is a mineralocorticoid hormone secreted by the adrenal cortex. Increased aldosterone stimulates the reabsorption of sodium, which also increases the loss of potassium and hydrogen ion to the urine. Finally, water is reabsorbed in the collecting duct through special pores that are regulated by antidiuretic hormone, which is released by the posterior pituitary. ADH increases the permeability of the collecting duct to water, which leads to increased water reabsorption.

tion, more concentrated urine, and reduced urine outflow (antidiuresis). Nearly all of the sodium originally filtered is reabsorbed by the kidney, so that less than 1% of originally filtered sodium remains in the final urine.¹⁵

2.3.2 Mechanism of Diuretic Drugs

Diuretic drugs will increase urine output by the kidney. This is accomplished by altering how the kidney handles sodium. If the kidney excretes more sodium, then water excretion will also increase. Most diuretics produce diuresis by inhibiting the reabsorption of sodium at different segments of the renal tubular system. Sometimes a combination of two diuretics is given because this can be significantly more effective than either compound alone (synergistic effect). The reason for this is that one nephron segment can compensate for altered sodium reabsorption at another nephron segment; therefore, blocking multiple nephron sites significantly enhances efficacy.¹⁶

• Loop Diuretics

Loop diuretic action by inhibit the sodium-potassium-chloride cotransporter in the thick ascending limb. This transporter normally reabsorbs about 25% of the sodium load; therefore, inhibition of this pump can lead to a significant increase in the distal tubular concentration of sodium, reduced hypertonicity of the surrounding interstitium, and less water reabsorption in the collecting duct. This altered handling of sodium and water leads to both diuresis (increased water loss) and natriuresis (increased sodium loss). By acting on the thick ascending limb, which handles a significant fraction of sodium reabsorption, loop diuretics are very powerful diuretics. These drugs also induce renal synthesis of prostaglandins, which contributes to their renal action, including the increase in renal blood flow and redistribution of renal cortical blood flow.¹⁷

• Thiazide Diuretics

Thiazide diuretics, which are the most commonly used diuretic, inhibit the sodium-chloride transporter in the distal tubule. Because this transporter normally only reabsorbs about 5% of filtered sodium, these diuretic are less efficacious than loop diuretics in producing diuresis and natriuresis. Nevertheless, they are sufficiently powerful to satisfy many therapeutic needs requiring a diuretic. Their mechanism depends on renal prostaglandin production.⁶

Because loop and thiazide diuretics increase sodium delivery to the distal segment of the distal tubule, this increases potassium loss (potentially causing hypokalemia) because the increase in distal tubular sodium concentration stimulates the aldosterone-sensitive sodium pump to increase sodium reabsorption in exchange for potassium and hydrogen ion, which are lost to the urine. The increased hydrogen ion loss can lead to metabolic alkalosis. Part of the loss of potassium and hydrogen ion by loop and thiazide diuretics results from activation of the RAA system that occurs because of reduced blood volume and arterial pressure. Increased aldosterone stimulates sodium reabsorption and increases potassium and hydrogen ion excretion into the urine.¹⁸

• Potassium-sparing Diuretics

There is a third class of diuretic that is referred to as potassium-sparing diuretics. Unlike loop and thiazide diuretics, some of these drugs do not act directly on sodium transport. Some drugs in this class antagonize the actions of aldosterone (aldosterone receptor antagonists) at the distal segment of the distal tubule. This causes more sodium (and water) to pass into the collecting duct and be excreted in the urine.¹⁸ They are called K⁺-sparing diuretics because they do not produce hypokalemia like the loop and thiazide diuretics. The reason

for this is that by inhibiting aldosterone-sensitive sodium reabsorption, less potassium and hydrogen ion are exchanged for sodium by this transporter, and therefore less potassium and hydrogen are lost to the urine. Other potassium-sparing diuretics directly inhibit sodium channels associated with the aldosterone-sensitive sodium pump and it have similar effects on potassium and hydrogen ion as the aldosterone antagonists. Their mechanism depends on renal prostaglandin production. Because this class of diuretic has relatively weak effects on overall sodium balance, they are often used in conjunction with thiazide or loop diuretics to help prevent hypokalemia.¹⁹

• Carbonic Anhydrase Inhibitors

Carbonic anhydrase inhibitors inhibit the transport of bicarbonate out of the proximal convoluted tubule into the interstitium, which leads to less sodium reabsorption at this site and, therefore, greater sodium, bicarbonate and water loss in the urine. These are the weakest of the diuretics and seldom used in cardiovascular disease. Their main use is in the treatment of glaucoma.²⁰

2.4 Diuretic Resistance

The general definition refers to the failure to achieve effective congestion relief despite appropriate or escalating doses of diuretics. It can be defined by inadequate response to diuretic therapy (e.g., failure to lose 0.5-1kg of weight per day) when the following measures are ensured: the absence of third space overload with intravascular volume depletion, dietary salt restriction (fractional excretion of sodium <2%) and discontinuation of nonsteroidal anti-inflammatory drugs. Some early reports estimated the prevalence of diuretic resistance to be 20%-30% among HF patients. However, the lack of a formal definition makes it impossible to properly assess the numbers.¹

2.4.1 Pathophysiology of Diuretic Resistance

The pathophysiology of diuretic resistance is very complex, and several etiologies may be involved. It derives from multiple factors, including reduced delivery of the diuretic to its luminal site of action, neurohormonal activation, tubular compensatory adaptation, and drug interactions.⁶

• Reduced Delivery of the Diuretic to its site of Action

Reduced delivery of the diuretic to its site of action is closely related to its decreased bioavailability. In HF patients, increased peripheral and bowel wall edema leads to reduced absorption of the diuretic, with a more marked effect when oral furosemide is used.¹

HF itself, as well as concurrent chronic kidney disease (CKD) (urate and other competing organic acids), may lead to decreased glomerular filtration rate, which in turn leads to impaired secretion of diuretics by the organic acid transporter into the proximal tubule. Reduced glomerular filtration rate can, therefore, reduce delivery or reduce the active secretion of loop diuretics into their site of action. Moreover, CKD has been proposed as a contributing factor to the development of HF overall, regardless of left ventricular ejection fraction. CKD leads to volume retention, altered calcium-phosphate metabolism, hyperparathyroidism, vitamin D deficiency, anemia, and the accumulation of uremic toxins.³

Renal dysfunction caused by intra-abdominal hypertension and cardiorenal syndromes is also a plausible mechanism of diuretic resistance through venous congestion. Intra-abdominal hypertension relief improves renal perfusion, renal filtration, and diuresis. It is usually present in up to 60% of acutely decompensated HF patients. It is very important to emphasize the need to detect third-space overload

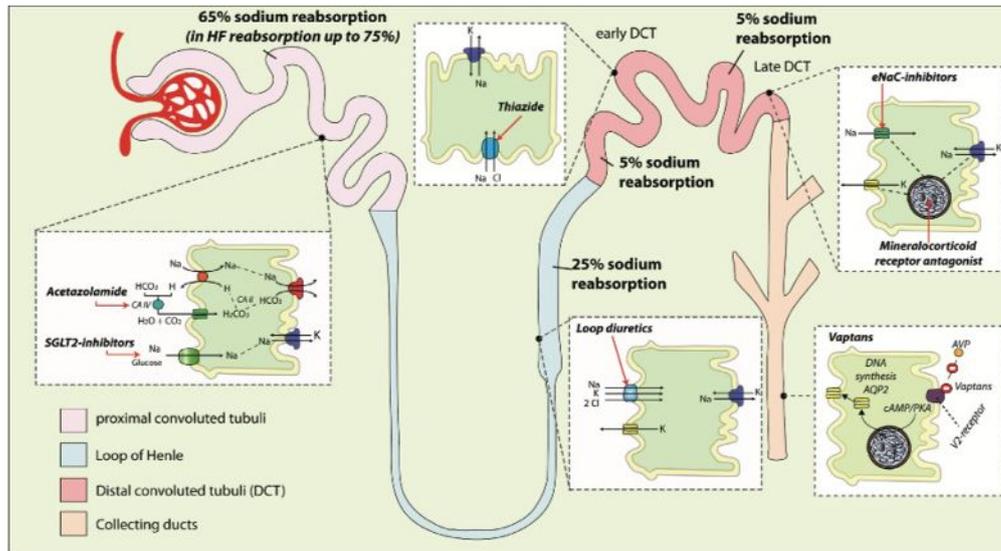


Figure 1. Sites and Mode of Action and Effects on Sodium Reabsorption in the Nephron of Different Diuretics

as opposed to intravascular overload because both the kidneys and diuretic therapy can only act in vascular overload.⁴

Persistent diuretic use in patients who are already suffering from intravascular volume depletion further activates the renin-angiotensin-aldosterone (RAA) axis and makes diuretic resistance dependent on renal blood flow. Sodium and chloride measurements may indicate when the vascular volume has been optimized because they decrease as euvolemia approaches. These may serve as more reliable markers of decongestion as opposed to the clinical signs and symptoms traditionally used to guide decongestive therapy.⁷ Clinical signs and symptoms lack sensitivity and specificity but do raise the need for further clinical evaluation. Natriuretic peptides are helpful for diagnosis and prognosis but lack the power to properly monitor volume status. Newer approaches point to quantitative blood volume analysis as a means to differentiate hypervolemia profiles. Appropriate profiling of volume overload in HF, according to blood volume, has therapeutic implications and may aid patients with diuretic resistance, redirecting them to other forms of decongestion.⁴

Another mechanism of diuretic activity impairment involves increased reabsorption of sodium and chloride in the proximal tubule, leading to decreased delivery of these substrates to the distal areas of the nephron where loop diuretics act. This mechanism causes diuretic resistance through decreased substrate availability to the sodium-potassium-chloride cotransport system.⁹

Albumin levels also correlate to diuretic action because they are high-affinity albumin-binding molecules more than 90%. Hypoalbuminemia increases the drug distribution volume and prevents suitable kidney delivery. On the other hand, high levels of albuminuria decrease loop diuretic delivery. Increased urine albumin binds to diuretics, preventing their ligation to the sodium-potassium-chloride receptors and thus impairing their action.²⁰

• *Neurohormonal Activation*

Neurohormonal activation is strongly related to RAA axis upregulation. Loop diuretics can activate the RAA axis through a variety of mechanisms. They induce renin secretion through the direct blockade of the macula densa sodium-potassium-chloride cotransport system, thus leading to increased renin and aldosterone in a volume-independent pathway. Furthermore, diuretics induce renal prostacyclin production, which increases renin secretion. Finally, diuretics induce

volume contraction, thus activating renin secretion through vascular stimulation. RAA axis activation eventually leads to increased sodium reabsorption, prompting the onset of post-diuretic sodium retention and the braking phenomenon.²¹

Post-diuretic sodium retention is one of the processes through which diuretic resistance may be established, and it arises as soon as the concentration of diuretic in the tubular fluid drops below the therapeutic threshold. A negative net sodium balance in the 24 hours between natriuresis and post-diuretic sodium retention may not be achieved in the event of dietary non-compliance, rendering the diuretic effect insignificant. The braking phenomenon, on the other hand, is defined as the decrease in diuresis volume after multiple same-dose administrations of diuretic. This is linked to RAA axis activation and compensatory changes in the nephron.⁹

• *Tubular Compensatory Readaptation*

Tubular readaptation is another mechanism that helps explain the reduced diuretic response. Owing to the above-mentioned activation of the RAA axis, as well as the braking phenomenon, proximal tubular reabsorption arises, leading to increased sodium uptake in this area of the nephron. Simultaneously, the chronic use of loop diuretics, which inhibit sodium uptake in the loop of Henle, leads to increased sodium delivery to the distal tubular system, resulting in compensatory hyperplasia and hypertrophy. This means that the patient would retain more sodium and thus water than a diuretic-naïve patient. This resistance mechanism can be overcome using a sequential nephron blockade with thiazide diuretics.⁴

• *Drug Interactions*

Some drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs), can reduce the effect of diuretics. NSAIDs may cause diuretic resistance in a number of ways, particularly decreased prostaglandin synthesis, decreased renal vasodilation, increased renal reabsorption in areas of the nephron other than the loop of Henle and hypertension.⁹

Evidence regarding the effect of low-dose aspirin (<1 mg/kg/day) on a diuretic response, in particular, is more scarce and controversial. A previous study reported that chronic low-dose aspirin could profoundly affect platelet prostaglandin production without affecting diuretic-stimulated renal prostacyclin production or plasma renin activity. However, Jhund et al. demonstrated that the dilatation

on vena could occur following furosemide administration could be inhibited by both high and low dose-aspirin. Furthermore, Hall noted an important reduction in the need for diuretics when daily aspirin administration was stopped. There is also some evidence that aspirin, even at a low dose, may neutralize the favorable effects of angiotensin-

converting enzyme inhibitors by blocking prostaglandin production and enhancing the vasoconstrictor potential of endothelin. In patients with HF, aspirin should be avoided wherever possible, and other antithrombotic agents that respect the integrity of prostaglandin metabolism should be considered²².

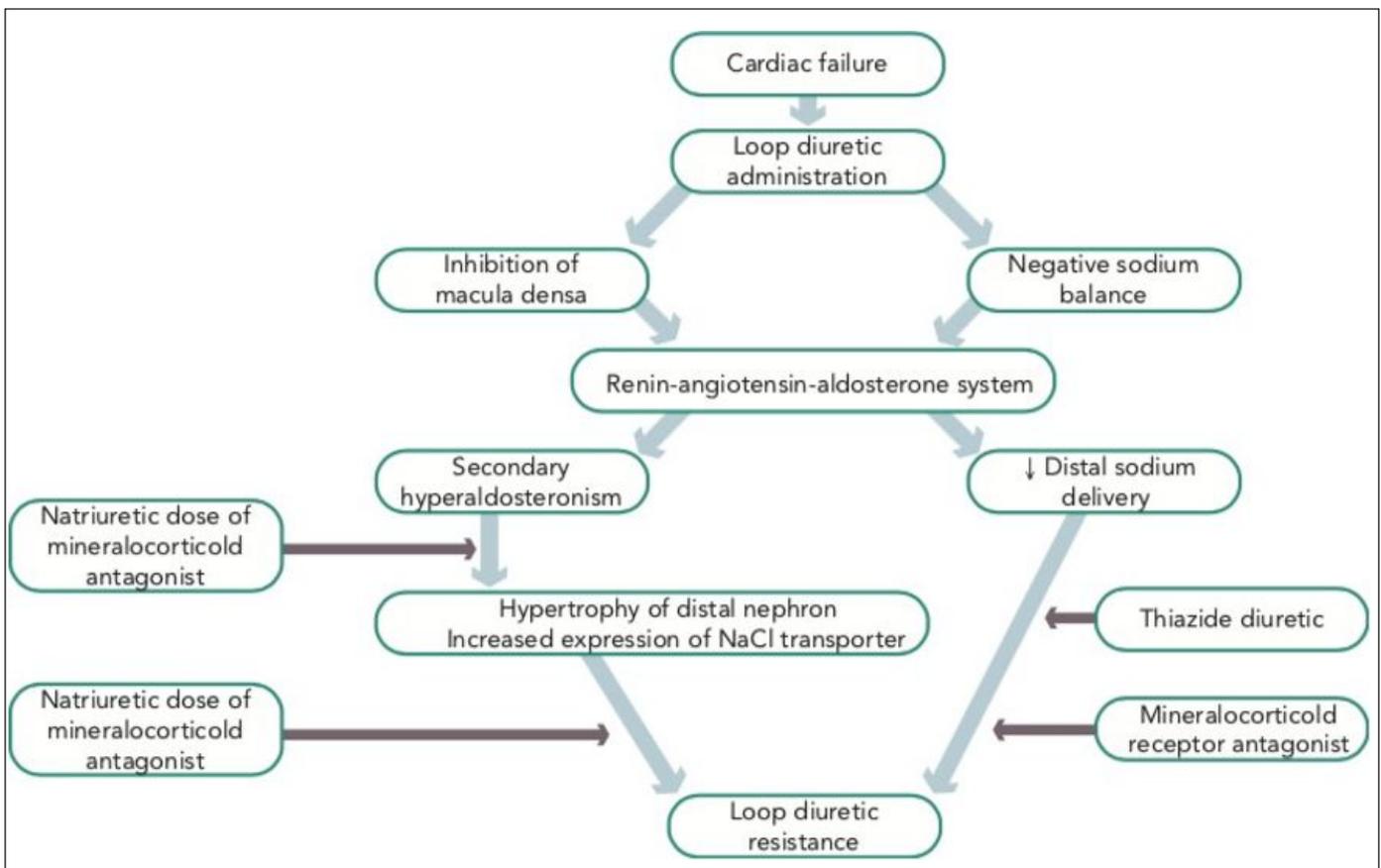


Figure 2. Mechanism of Diuretic Resistance in Heart Failure.¹¹

2.4.2 Management for Diuretic Resistance

• Salt Restriction

Dietary sodium restriction is a key determinant of diuretic efficacy. When dietary sodium intake is high, post-diuretic sodium retention compensates almost entirely for the loop-diuretic-induced sodium loss. Conversely, if sodium intake is restricted, post-diuretic sodium retention is minimized, resulting in a negative fluid and sodium balance. Thus, restricting sodium intake to less than 100 mEq/day mitigates the effect of post-diuretic sodium retention and helps achieve a negative sodium balance. A 24-hour urinary sodium excretion of more than 100 mEq/day or fractional excretion of sodium value >2% indicates non-compliance with sodium restriction and rules out true diuretic resistance.⁹

• Discontinue concomitant use of nonsteroidal anti-inflammatory drugs

Concomitant use of NSAIDs is a major cause of diuretic failure, and discontinuing them can significantly improve diuretic effectiveness.⁹

• Establish the Effective Single Dose

Diuretics have a dose-response curve, and the effect only begins once the diuretic level reaches a therapeutic threshold within the

renal tubular lumen. In conditions such as CKD and cardiorenal syndrome, the dose-response curve shifts downwards and towards the right. This means that these patients need higher doses of loop diuretics to achieve the therapeutic drug level at the site of action. Diuretic doses below said threshold are ineffective, so a higher effective single loop diuretic dose is needed rather than administering an inadequate dose more frequently.⁴

• Increase the dose frequency of loop diuretics

Because most loop diuretics are short-acting, increasing the dose frequency can help overcome post-diuretic sodium retention and restore diuretic response.⁴

• Diuretic Substitution

Gastrointestinal absorption and the bioavailability of different diuretics belonging to the same class can vary considerably, and this could be a factor behind a poor response. Furosemide has a bioavailability of about 50%, whereas torsemide and bumetanide have almost completed absorption (80-100%). At times, replacing furosemide with comparable doses of bumetanide or torsemide can be enough to improve diuresis.⁵

• Intravenous Diuretics

Sometimes, administering diuretics intravenously instead of orally is all that is needed to improve diuresis. Oral absorption may be altered in the presence of gastrointestinal edema, gastroparesis, and delayed gastric emptying. Drug concentration at the site of diuretic action in the tubule lumen may be inadequate due to decompensated HF, renal hypoperfusion, or impaired secretion as a result of hypoalbuminemia.²³

Compared to bolus doses, continuous diuretic infusion may be more effective in improving diuresis. It may decrease fluctuations in intravascular volume, resulting in a more gradual and relatively constant hourly urine output and limiting the effect of post-diuretic sodium retention. Some studies found that furosemide administered as a continuous infusion was more effective than intermittent bolus doses since significantly less furosemide was required to produce the same diuresis and due to the elimination of a diuretic-free interval (during which compensatory sodium retention occurs).⁵ In the Diuretic Optimization Strategies Evaluation (DOSE) trial, there were no significant differences in patients' global symptom assessment or in the change in renal function between the two strategies.²⁴

• Sequential Nephron Blockade

A sequential sodium uptake blockade in different nephron segment by means of a combination of two or more diuretics from different classes may produce an additive or synergistic mechanism of action and diuretic response and can be an effective approach in resistant cases.¹⁴

Table 1. Combination diuretic therapy²⁵

To an effective or maximal safe dose of a loop diuretic add:
<i>Distal convoluted tubule diuretics</i>
Metolazone 2.5-10 mg per os daily (duration or frequency adjusted based on the target weight)
Hydrochlorothiazide (or equivalent) 25-100mg os daily
Chlorothiazide 500-1000 mg intravenously
<i>Proximal tubule diuretics</i>
Acetazolamide 250-375 mg daily or up to 500 mg intravenously
<i>Potassium-sparing diuretics</i>
Spirolactone 100-200 mg daily
Amiloride 5-10 mg daily

• Management of intraabdominal pressure

Intra-abdominal hypertension is defined as a sustained intra-abdominal pressure of 12 mmHg or above. Splanchnic and interstitial congestion may cause elevated intra-abdominal pressure in the absence of ascites in acute decompensated HF. In such patients, a rise in intra-abdominal pressure increases renal venous pressure, thereby reducing the transanal perfusion gradient and renal perfusion. Elevated intra-abdominal pressure also causes increased renal interstitial pressure that opposes net filtration pressure. Both contribute to renal impairment and diuretic resistance.⁹ When intravenous loop diuretic therapy fails, measuring intra-abdominal pressure is an inexpensive and minimally invasive procedure that rules out a diuretic resistance cause. If intra-abdominal hypertension or abdominal compartment syndrome (defined as a sustained intra-abdominal pressure of >20 mmHg, which is associated with new organ dysfunction) is identified, a reduction in intra-abdominal pressure by mobilizing third-space fluid can be achieved through a combination of diuretics, vasodilators and/or inotropes. Abundant ascites can be managed with paracentesis, ultrasound, or computer tomography guidance if

needed. In certain patients, ultrafiltration (UF) may be appropriate. The therapeutic aim is to achieve an abdominal perfusion pressure (calculated as the mean arterial pressure minus the intra-abdominal pressure) of over 60 mmHg (with an intra-abdominal pressure of 5 to 7 mmHg), which signifies a favorable outcome (improvement in renal perfusion, renal filtration, and diuresis).²⁴

• Infusion with Albumin

Simultaneous infusion of a diuretic and albumin could slightly improve diuretic resistance. A meta-analysis of eight randomized clinical trials of adults with hypoalbuminemia, comparing the co-administration of loop diuretics and albumin versus loop diuretics alone, found transient effects of modest clinical significance with the former strategy. However, this intervention should only be considered in severely hypoalbuminemia patients when the approaches discussed above have failed.²³

• Renal Dose Dopamine

Low doses of dopamine (<3 mcg/kg/min) selectively work on peripheral dopaminergic receptors resulting in vasodilation in the renal, coronary, splanchnic, and cerebral circulations. Two recent trials of dopamine in acute HF - the Dopamine in Acute Decompensated Heart Failure II (DAD-HF II) trial and the Renal Optimization Strategies Evaluation (ROSE) trial - have shown no added benefit with the addition of dopamine to standard therapy with high-dose diuretics. Thus, on the basis of current data, dopamine has no role in nonhypotensive patients with acute HF.²⁴

• Alternative Pharmacological Therapies

Hypertonic saline works osmotically to pull free water from the interstitial fluid into the renal vasculature. In addition, to increase renal blood flow, it improves sodium delivery to the loop of Henle, thus restoring some of the loop diuretics' effect. Several studies have reported better diuresis, improved renal function and shorter hospital stay when hypertonic saline is added to loop diuretic therapy.⁴

Glucocorticoids may promote diuresis and protect renal function in patients with acute HF. Liu et al. reported the effects of prednisolone in 13 congestive HF patients with significant volume overload and diuretic resistance who had failed to respond to a conventional sequential nephron blockade treatment strategy. They reported an improvement in diuresis, clinical status, and renal function.²⁵

Levosimendan was studied in patients presenting with acute HF in the Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy (REVIVE) studies. These showed that levosimendan improved renal function and diuretic response in such patients. However, there was also an increased risk of arrhythmia and hypotension.²²

Nesiritide is a synthetic B-type natriuretic peptide (BNP) approved by the Food and Drug Administration for symptomatic relief due to its favorable effects on hemodynamics, dyspnea, and renal function. However, both the ROSE trial and ter Maaten et al. (2015) found no additive effect of using low-dose nesiritide added to diuretic therapy in terms of decongestion or improved renal function. Experimental research has shown that renal delivery of BNP had significantly greater beneficial effects than systemic delivery. It could be that a higher systemic dose is needed; however, the usage there of would increase the incidence of adverse effects such as hypotension.²⁶

Vasopressin-2-receptor antagonists may promote aquaresis by blocking the effects of vasopressin on the vasopressin-2-receptors located in the collecting ducts, thus blocking the reabsorption of free water. This promotes water clearance without affecting sodium

balance. In the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial, tolvaptan at a dose of 30 mg once daily for a minimum of 60 days had no effect on total mortality or HF hospitalization when compared to placebo.²⁵

• Ultrafiltration

UF is very effective at removing plasma fluid from blood across a semipermeable membrane that allows small molecules to pass through along its pressure gradient to the ultrafiltrate fluid. Small studies suggest that UF improves pulmonary and peripheral edema, lung function, and hemodynamics without adverse effects on renal function. The fluid removal rate is reevaluated using clinical assessment and serial hematocrit measurements to ensure appropriate vascular compartment refill. The recent development of venovenous peripheral UF has positioned this technique as a potential alternative to loop diuretics in acute HF.⁹

3. Conclusion

The pathophysiology of diuretic resistance is very complex, and several etiologies may be involved. It derives from multiple factors, including reduced delivery of the diuretic to its luminal site of action, neurohormonal activation, tubular compensatory adaptation, and drug interactions.⁶ Diuretic resistance has emerged as an independent factor behind worse HF patient outcomes, namely in-hospital worsening, early post-discharge mortality, and rehospitalizations. Once the diuretic resistance has been treated successfully, the treatment of advanced HF should be optimized in order to reduce further morbidity and mortality. So, it is important for clinicians to diagnose diuretic resistance in advanced heart failure in order to have comprehensive management.

4. Declaration

4.1. *Ethics Approval and Consent to participate*
Not applicable.

4.2. *Consent for publication*
Not applicable.

4.3. *Availability of data and materials*
Data used in our study were presented in the main text.

4.4. *Competing interests*
Not applicable.

4.5. *Funding source*
Not applicable.

4.6. *Authors contributions*
Idea/concept: MSR, ASS. Design: ASS. Control/supervision: MSR, QP, BS. Data collection/processing: ASS. Extraction/Analysis/interpretation: ASS. Literature review: MSR. Writing the article: ASS. Critical review: MSR. IP. BS. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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